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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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EXAMINER

MYERS, CARLA J

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 08/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

| | | |
|-----------------|-----------------|----------|
| Application No. | GONZALGO ET AL. | |
| 09/887,941 | Examiner | Art Unit |
| | Carla Myers | 1634 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 28 May 2004.
2a) This action is **FINAL**. 2b) This action is non-final.
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 11-18 and 22 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 11-18 and 22 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____

5) Notice of Informal Patent Application (PTO-152)
6) Other: _____

DETAILED ACTION

1. This action is in response to the amendment filed May 28, 2004. Claims 11-18 and 22 are pending. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

THE FOLLOWING CONSTITUTES NEW / MODIFIED GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS:

Claim Rejections - 35 USC § 112

2. Claims 11-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

A. With respect to claims 11-17 and 22, the specification as originally filed does not provide basis for the concept set forth in the claims of any "labeled dNTPs" or dNTPs that are labeled with "radiolabels or fluorescent labels and combinations thereof". The specification as originally filed provides basis for ³²P labeled dNTPs and basis for methods which utilize a combination of ³²P labeled dNTPs. The specification also states that fluorescent probes may be utilized in the disclosed method. However, there is no basis in the specification to support the amendment to the claims to recite generically that the dNTPs are labeled with

any label or to recite that the dNTPs are labeled with any combination of radiolabels and fluorescent labels.

Response to Arguments:

In the response filed May 28, 2004, Applicants traversed the previous grounds of rejection by stating that Applicants were in possession of the full scope of the claimed invention at the time of filing because the specification as originally filed teaches the use of ^{32}P labeled dNTPs. It is asserted that because the specification teaches the use of ^{32}P labeled dNTPs one would understand that the dNTPs could be labeled in any way that would allow for the relative quantification of a C:T ratio.

Applicant's arguments have been fully considered but are not persuasive because the teachings regarding ^{32}P labeled dNTPs does not provide basis for the broader concept of labeling dNTPs with any type of label and does not provide basis for the concept of using a combination of radioactive and fluorescent labels or a combination of different types of fluorescent labels.

B. With respect to claims 17 and 18, the specification as originally filed does not provide basis for the concept of primers which are "bisulfite-converted sequences corresponding to SEQ ID NO: 1-12." The specification does not define this phrase and does not refer to primers in terms of the fact that they correspond to SEQ ID NO: 1-12. It is not clear as to what is intended to be encompassed by this phrase. However, it appears that this phrase includes variants of the recited sequence which have been treated with sodium bisulfite or which have modified at cytosine residues or which have been otherwise modified

in their sequence. There is no basis in the specification for such modified primers or for primers which correspond in some manner to SEQ ID NO: 1-12. The specification teaches modifying the genomic DNA with sodium bisulfite, but does not teach primers having a sequence distinct from that of SEQ ID NO: 1-12.

Response to Arguments:

In the response filed May 28, 2004, Applicants traversed the previous grounds of rejection by stating that Applicants were in possession of the invention as claimed because the specification teaches that bisulfite converts unmethylated cytosine to uracil, followed by conversion to thymine during the amplification reaction. Applicants argue that the specification teaches that the Ms-SNuPE primer is designed to hybridize to a region of bisulfite-treated DNA," the sequence of which is not changed by the bisulfite-treatment. However, the invention is not limited to the preferred embodiments."

Applicant's arguments have been fully considered but are not persuasive. While the specification as originally filed does teach that bisulfite converts unmethylated cytosine to uracil and that primer extension of this sequence results in the incorporation of a thymine into the primer extension product, the specification does not teach the concept of sequences "corresponding" to SEQ ID NO: 1-12. Applicants state that the invention is not limited to the preferred embodiments. However, the specification as originally filed does not teach that the sequence of the primer may differ from SEQ ID NO: 1-12 in a manner other than that which results directly from bisulfite treatment of the sequence. The language "corresponding" is not defined in the specification and thereby has

been given its broadest reasonable scope. As such the claims are inclusive of primers which share any level of complementarity or identity with the sequences set forth in SEQ ID NO: 1-12. However, the specification as originally filed does not provide basis for this genus of primers.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17 and 18 are indefinite over the recitation of "bisulfite-converted sequences corresponding to SEQ ID NO: 1-12" because it is unclear as to what is intended to be encompassed by this phrase. The term "corresponding" is not defined in the specification or in the art and is not referred to in the specification. It is unclear as to how the term "corresponding" is intended to characterize the relationship between the bisulfite-converted sequences and the sequences of SEQ ID NO: 1-12. It is unclear as to what degree of sequence identity or complementarity is shared between the primers of SEQ ID NO: 1-12 and the corresponding bisulfite-converted sequences.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re*

Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-18, and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,251,594. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '594 are inclusive of methods of determining the DNA methylation status of a genomic DNA sample by assaying for the methylation state at the cytosine residue of the CpG dinucleotide sequences by measuring the incorporation of labeled dNTPs. The present claims recite generally that the dNTPs are labeled, whereas the claims of '594 specifically recite labeling the dNTPs with ^{32}P . Accordingly, the presently claimed method encompasses detecting the use and detection of ^{32}P -labeled dNTPs. Additionally, both the present claims and the claims of '594 encompass Ms-SNuPE primers comprising SEQ ID NO: 1-12.

Response to Arguments:

In the response filed May 28, 2004, Applicants state that the present application is commonly owned with the '594 patent and "applicants are thus prepared to file a timely Terminal Disclaimer in compliance with 37 C.F.R. 3.73(b)

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upon the Examiner's indication of allowable subject matter. Applicants have not yet filed a terminal disclaimer. Accordingly, the rejection is maintained for the reasons of record.

5. Claims 11-18 and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23, 24, 29-36 of copending Application No. 10/109,725. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '725 are inclusive of methods of determining the DNA methylation status of a genomic DNA sample by assaying for the methylation state of more or more CpG dinucleotide sequences within a sequence that hybridizes to any one of SEQ ID NO: 1-12.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments:

In the response filed May 28, 2004, Applicants state that the present application is commonly owned with the '725 application and "applicants are thus prepared to file a timely Terminal Disclaimer in compliance with 37 C.F.R. 3.73(b) upon the Examiner's indication of allowable subject matter. Applicants have not yet filed a terminal disclaimer. Accordingly, the rejection is maintained for the reasons of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. This phone number will be changed after January 13 to (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. This number will be changed after January 22 to (571) 272-0782. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
August 17, 2004

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER